

CLAIMS

1. A transgenic *Pichia pastoris* comprising at least one of a presenilin 1, APH-1, nicastrin, or PEN-2 encoding transgene.
2. The *Pichia pastoris* of claim 1, further comprising a transgene encoding β -Amyloid Precursor Protein or a derivative of β -Amyloid Precursor Protein.
3. The *Pichia pastoris* of claim 2, further defined as comprising a transgene encoding a derivative of β -Amyloid Precursor Protein.
4. The *Pichia pastoris* of claim 3, wherein the derivative of β -Amyloid Precursor Protein is APP C99.
5. The *Pichia pastoris* of claim 1, further defined as comprising a presenilin 1 encoding transgene.
6. The *Pichia pastoris* of claim 5, wherein the presenilin 1 is epitope tagged.
7. The *Pichia pastoris* of claim 6, wherein the epitope tag is a Tandem Affinity Purification tag.
8. The *Pichia pastoris* of claim 5, wherein the presenilin 1 is a mutant presenilin 1.
9. The *Pichia pastoris* of claim 8, wherein the mutant presenilin 1 is M146L, E280A, G384A, or D385A.
10. The *Pichia pastoris* of claim 8, wherein the mutant presenilin 1 is epitope tagged.
11. The *Pichia pastoris* of claim 10, wherein the epitope tag is a Tandem Affinity Purification tag.
12. The *Pichia pastoris* of claim 1 further defined as comprising presenilin 1, APH-1, nicastrin, and PEN-2 encoding transgenes.
13. The *Pichia pastoris* of claim 12 further defined as exhibiting γ -secretase activity.

14. The *Pichia pastoris* of claim 12 wherein the presenilin 1 is a mutant presenilin 1.
15. The *Pichia pastoris* of claim 14 wherein the mutant presenilin 1 comprises a M146L, E280A, or G384A mutation.
16. The *Pichia pastoris* of claim 15 further defined as exhibiting γ -secretase activity.
17. The *Pichia pastoris* of claim 14 wherein the mutant presenilin 1 comprises a D385A mutation.
18. The *Pichia pastoris* of claim 17 further defined as exhibiting no γ -secretase activity.
19. A method of producing a transgenic *Pichia pastoris* with γ -secretase activity comprising providing the *Pichia pastoris* with a transgene encoding presenilin 1, APH-1, nicastrin, and PEN-2.
20. A method of identifying a compound that inhibits γ -secretase activity comprising:
 - a) preparing a solubilized membrane preparation from a transgenic *Pichia pastoris* comprising presenilin 1, APH-1, nicastrin, and PEN-2 encoding transgenes, wherein the *Pichia pastoris* exhibits γ -secretase activity;
 - b) contacting the solubilized membrane preparation with a substrate for γ -secretase and a test compound; and
 - c) determining whether γ -secretase activity is decreased in the presence of the test compound, the decrease in γ -secretase activity being an indication that the test compound inhibits γ -secretase activity.
21. The method of claim 20 further comprising isolating γ -secretase away from the solubilized membrane preparation.
22. The method of claim 20, wherein the substrate for γ -secretase is β -Amyloid Precursor Protein or a derivative of β -Amyloid Precursor Protein.
23. A method of identifying a compound that inhibits γ -secretase activity comprising:

- a) contacting a transgenic *Pichia pastoris* comprising presenilin 1, APH-1, nicastrin, PEN-2, and amyloid precursor protein encoding transgenes, wherein the *Pichia pastoris* exhibits γ -secretase activity, with a test compound; and
- b) determining whether γ -secretase activity is decreased in the presence of the test compound, the decrease in γ -secretase activity being an indication that the test compound inhibits γ -secretase activity.

24. The method of claim 23, wherein the substrate for γ -secretase is β -Amyloid Precursor Protein or a derivative of β -Amyloid Precursor Protein.